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PERSPECTIVE

Supplemental thiamine as a practical, potential way to prevent Alzheimer's disease from commencing

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Abstract

It is better to attempt stopping Alzheimer's disease (AD) before it starts than trying to cure it after it has developed. A cerebral scan showing deposition of either amyloid or tau identifies those elderly persons whose cognition is currently normal but who are at risk of subsequent cognitive loss that may develop into AD. Synaptic hypometabolism is usually present in such at-risk persons. Although inadequate adenosine triphosphate (ATP) may cause synaptic hypometabolism, that may not be the entire cause because, in fact, measurements in some of the at-risk persons have shown normal ATP levels. Thiamine deficiency is often seen in elderly, ambulatory persons in whom thiamine levels correlate with Mini-Mental State Examination scores. Thiamine deficiency has many consequences including hypometabolism, mitochondrial depression, oxidative stress, lactic acidosis and cerebral acidosis, amyloid deposition, tau deposition, synaptic dysfunction and abnormal neuro-transmission, astrocyte function, and blood brain barrier integrity, all of which are features of AD. Although the clinical benefits of administering supplementary thiamine to patients with AD or mild cognitive impairment have been mixed, it is more likely to succeed at preventing the onset of cognitive loss if administered at an earlier time, when the number of aberrant biochemical pathways is far fewer. Providing a thiamine supplement to elderly persons who still have normal cognition but who have deposition of either amyloid or tau, may prevent subsequent cognitive loss and eventual dementia. A clinical trial is needed to validate that possibility.

KEYWORDS
Alzheimer's, cognitive loss, commencement, early, prevent, thiamine

1 | INTRODUCTION

The optimum approach to Alzheimer's disease (AD) dementia is to prevent it before it begins, not when it has already developed. AD begins when cognitive loss, of which a major accompaniment is synaptic dysfunction/loss, first appears. Those elderly persons with cognition that is currently normal but who are at risk of subsequent AD have synaptic hypometabolism as demonstrated by reduced cerebral uptake of ^{18}F-deoxyglucose (^{18}F-FDG), and scans showing an increased cerebral amount of either amyloid, amyloid beta (Aβ) oligomers, or tau protein. Although systemic inputs to cognitive loss include cerebral microvascular and macrovascular pathology, hypertension, diabetes, genetic factors, environmental exposures, head trauma, smoking, and homocysteinemia, it is argued here that synaptic hypometabolism, mitochondrial depression, oxidative stress, lactic acidosis and cerebral acidosis, amyloid deposition, tau deposition, synaptic dysfunction and abnormal

neurotransmission, astrocyte function, and blood brain barrier (BBB) integrity, are the main antecedent, biochemical pathways that initiate the synaptic dysfunction that causes cognitive loss. Although that perhaps oversimplifies what is a complex situation, it has heuristic value because thiamine, a non-prescription medication, might correct many of the above elements that contribute to the initiation of cognitive loss and thus act as a preventative. If that were validated in a clinical trial, then prevention of AD would be a practical possibility.

Synaptic hypometabolism may be the earliest detectable abnormality in some elderly persons who have currently normal cognition but who develop loss of cognition at some later date. For example, in one of the earliest demonstrations, Kennedy et al. saw a significant reduction in cerebral metabolic rate of glucose in 24 asymptomatic but at-risk individuals from families with AD, compared to 16 age-matched controls.[1] That has subsequently been well-confirmed by others.[2] On the other hand, why does a decrease in adenosine triphosphate (ATP) formation, producing synaptic hypometabolism, not induce a compensatory mechanism? The answer may be that perhaps it does, but inadequately, as shown by both the ongoing hypometabolism and the eventual loss of cognition by some subjects. Another possibility, however, is that there is a mechanism additional to ATP that contributes to the hypometabolism. Thiamine is a strong candidate for that extra mechanism because it rivals ATP for being essential to many important aspects of the molecular biology that are relevant to the development of dementia. Sang et al. compared 14 patients with AD and 14 controls, and showed that in AD there were significantly lower results for blood levels of thiamine diphosphate ($P < .001$) and of glucose metabolism in the temporal cortex as assessed by ^{18}F-FDG cerebral scan ($P < .001$); and that glucose metabolism in the temporal cortex and blood thiamine diphosphate were correlated ($r = .64$, $P < .05$).[3] They then fed mice a thiamine-deficient diet and demonstrated that thiamine was reduced in both blood and brain ($P < .001$), and glucose metabolism became reduced in their hippocampus ($P < .05$), which would result in synaptic hypometabolism being shown by low uptake of ^{18}F-FDG. In the same publication, Sang et al. showed that cerebral glucose hypometabolism resulted from knockout (ko) in mice of the thiamine phosphokinase gene that phosphorylates thiamine.[3] Studies in cultured cells also show the importance of thiamine: in cells that overexpressed APPsw, a thiamine-deficient medium significantly increased the presence of Aβ in both the secreted culture medium and the cellular extract but after treatment with thiamine diphosphate, then concentrations of secreted and intracellular Aβ40 were increased more than 3-fold.[4] Further, the same authors showed that deficiency of thiamine diphosphate increased Aβ42 in the thalamus by 67% ($P < .001$) and in the hippocampus by 42.8% ($P < .05$). In fact, there is much evidence, presented in the remainder of this article, showing that thiamine or its variants act in multiple pathways affecting AD and mild cognitive impairment (MCI). Those pathways involve hypometabolism, mitochondrial depression, oxidative stress, lactic acidosis and cerebral acidosis, amyloid deposition, tau deposition, synaptic dysfunction and abnormal neuro-transmission, astrocyte function, and BBB integrity. Importantly and shown below, there is a substantial prevalence of thiamine deficiency in elderly persons; and the occasional success for thiamine treatment of patients with mild AD suggests that it might be successful in preventing subsequent AD if administered before the process causing cognitive loss has started to unfold, when fewer biochemical pathways are involved.

RESEARCH IN CONTEXT

Can one thiamine tablet a day keep Alzheimer's away? This article argues that it may do so. The multiple elements that contribute to pathogenesis of Alzheimer's dementia include mitochondrial depression, increased ROS, lactic acidosis and cerebral acidosis of the brain, cerebral depositions of amyloid and tau, synaptic dysfunction, disturbed neurotransmission, cognitive impairments, and disturbances affecting astrocytes, endothelial cells, and the blood brain barrier. Most of those elements of Alzheimer's pathogenesis are addressed by thiamine which, if used at a time when a middle-aged person still has normal cognition, may prevent those components of pathogenesis from developing. In brief: it is easier to prevent Alzheimer's than to try to reverse it after it has developed. The data supporting the prophylactic use of thiamine are robust. In order to validate its use, a clinical trial is advocated that would enroll persons aged 65 or older who have evidence of depositions of amyloid or tau in their brains, and randomly assign them to take, for as long as 5 years, either thiamine 100 mgs daily or a matched placebo tablet.

2 | FORMS OF THIAMINE AND THEIR EFFECTS IN THE BRAIN

Thiamine's chemical structure has a pyrimidine and thiazole group joined by a methylene bridge. In the body, thiamine is usually phosphorylated via thiamine phosphokinase, as a monophosphate (TMP), diphosphate (TDP), or triphosphate (TTP). There are three thiamine transporters, and there is also a mitochondrial transporter. Noteworthy is that both free thiamine and TMP cross the BBB.[5] Thiamine pyrophosphate is the cofactor for three important enzymes: pyruvate dehydrogenase (PDH), αketoglutarate dehydrogenase, and transketolase, the lack of each of which may cause impairment of brain metabolism and synaptic hypometabolism because each decarboxylates its substrate and transfers the resulting acyl group to coenzyme A (CoA), leading to regeneration of nicotinamide adenine dinucleotide hydride (NADH). Because pyruvate dehydrogenase requires thiamine pyrophosphate as cofactor, in thiamine deficiency pyruvate cannot undergo conversion to acetyl CoA; the excess pyruvate is then converted to lactate. α-ketoglutarate dehydrogenase catalyzes the oxidative decarboxylation of α-ketoglutarate to succinyl CoA, so in thiamine deficiency this is another cause of ATP reduction. Transketolase

catalyzes the reactions of the pentose phosphate pathway producing pentoses, NADH, and eventually ATP. The following equations show the pathways (with enzymes in parentheses):

acetyl-CoA→(acetyl-CoA synthetase)→AMP→+ inorganic phosphate (Pi)→ATP;

or acetyl-CoA→(phosphate acetyl transferase)→ATP;

or acetyl-CoA +oxaloacetate→ADP→ (+Pi)→ATP.

Regarding thiamine deficiency as a cause of impaired functions of pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, and transketolase, Gibson et al. examined the brains of nine patients with AD and ten controls.[6] In the AD brains, α-ketoglutarate dehydrogenase complex activity was reduced to 13% of the controls in the frontal cortex, to 8% of the controls in the occipital cortex, and was undetectable in the mid-temporal cortex; transketolase activity was 50% to 55% of that in controls in the frontal, mid-temporal, and occipital cortices ($P < .005$). α-ketoglutarate dehydrogenase complex has three subunits, EI, E2, and E3. Mastrogiacomo et al. measured protein levels of the three subunits in brains of 29 patients with AD and 29 control subjects. In the temporal cortex of the AD group, protein levels of all three subunits were significantly reduced by 23% to 41%.[7]

3 | THE PROBLEM OF ASSESSING NORMAL THIAMINE LEVELS

Knowing values for thiamine levels in a representative, normal population would be a useful guide for designating levels as either reduced or increased. The difficulty is that there are so many variables influencing the laboratory results that a normal range has to be published by the local facility and may not apply to a facility elsewhere. The variables include methodology of the assay and what biochemical form of thiamine is measured, whether red blood cells (RBC) or plasma was assayed, subjects' nutritional state, comorbidities, use of alcohol, and geographic locale. The older assay measured the rise in red blood cell transketolase (TK) induced by adding thiamine pyrophosphate (TPP; termed the TPP TK effect); that method gave unreliable results whereas high pressure liquid chromatography (HPLC) is more accurate. The important effect of geographical location is that in many high-income countries, foods may be fortified with thiamine but that may not occur in low- and middle-income countries where, in addition, the reliance on staple foods containing low amounts of thiamine may cause deficiency. Excessive consumption of alcohol causes severe impairment of intestinal absorption, and excessive use of alcohol is a well-known cause of thiamine deficiency that may produce Wernicke-Korsakoff syndrome; other reasons for deficiency include cooking, baking, and preserving foods, which can degrade thiamine; consumption of foods such as betel nut or tea leaves, which contain thiamine antagonists; and thiaminases in foods such as raw fish. Sulfites used in processed foods depress thiamine levels.[8] Severe obesity is another cause: persons with body mass index > 35 showed a 16.5% prevalence of thiamine deficiency.[9] Very few articles explain the basis for the range of normal they applied; one of them mentions an internal study using plasma from 116 adults age 19 to 64 years, showing a range of 4 to 15 nmol/L.[10] That study measured unphosphorylated thiamine in plasma whereas it mostly circulates in phosphorylated form, and plasma contains only ≈20% of the circulating thiamine while RBCs contain ≈80%. The same laboratory (ARUP, a reference laboratory in Utah, USA) also assays thiamine diphosphate in whole blood and, without indicating the subjects from which it was determined, gives a reference range of 70 to 180 nmol/L; the Mayo Clinic also assays RBC for thiamine diphosphate and, interestingly, publishes the identical reference range.

4 | LEVELS OF THIAMINE IN PERSONS WITH NORMAL COGNITION CORRELATE WITH MINI-MENTAL STATE EXAMINATION SCORES

Blood thiamine and thiamine diphosphate levels were measured in 611 non-demented individuals by Lu et al.[11] Thiamine diphosphate concentration showed a weakly positive correlation with Mini-Mental State Examination (MMSE) score ($r = 0.1492$, $P < .001$). They further analyzed the MMSE scores divided according to thiamine diphosphate level. Based on a cut-off level of 99.48 nmol/L (which was the lower value found by the authors to distinguish AD from controls), participants with a high thiamine diphosphate level performed better in Recall, as well as Attention and Calculation, than those with low levels. Particularly relevant in the present context are data from patients with MCI because they are closer to persons who have normal cognition. For example, Håglin et al. compared 32 MCI patients to 43 controls; plasma thiamine was 9.3 nmol/L in MCI, 18% lower than the 11.4 nmol/L in controls ($P = .028$); and thiamine monophosphate was 2.06 nmol/L in MCI, 43.9% lower than the 3.67 in controls ($P = .001$).[12]

The data provided in this paragraph and in the paragraph concerning thiamine in established AD, demonstrate the important part played by thiamine in the cerebral process underpinning cognitive loss.

5 | PREVALENCE OF THIAMINE DEFICIENCY IN ELDERLY POPULATIONS

As regards the effect of age, older persons often have more comorbidities and use more medications than younger ones but evidence suggests that neither of these affect thiamine levels,[13] although there is some evidence that diuretics may deplete thiamine.[14] The relevance of geographic locale and age is seen in a Belgian group of outpatients that had 10.5% of thiamine deficiency as assessed by the TPP TK method,[15] while an English group, mean age 77.7, free from disease and taking no medication, had a thiamine level measured in RBC by HPLC that was 25.8% higher than in the healthy young controls having a mean age of 26 years, although it was 67.7% lower in a group of institutionalized elderlies of mean age 82.8 years.[16] That study took the important precaution of excluding anyone who had used vitamin supplements in the past month or who drank > 7 units of alcohol per week. In New Zealand, Wilkinson et al. measured thiamine levels by HPLC in 221 ambulatory persons, mean age 76; their thiamine level was 32.1%

lower than in the 100 healthy controls of mean age 41.5 years,[13] and a subgroup of 39 with no active medical problems and taking no medications had a mean thiamine level that was almost identical to that in the 182 with comorbidities. For a list of nine commonly used medications, the thiamine pyrophosphate levels were similar between those taking and those not taking each medicine; unsurprisingly, the thiamine level for those not taking multivitamins was 24.2% lower than for those taking them. In brief: even using a more accurate laboratory method, elderly patients have been found to have either increased or decreased thiamine levels and as a result, it is uncertain what effect age has on thiamine levels.

6 | THIAMINE DEFICIENCY CAUSES MITOCHONDRIAL DEPRESSION

Most of the enzyme deficiencies associated with thiamine deficiency and described in the text of this article, derive from mitochondrial function and, therefore, reflect its depressed function. That is also shown by studies of isolated mitochondria. Neuroblastoma cells grown in a thiamine deficient medium had at least 25% of mitochondria that were swollen and translucent by electron microscopy.[17] ATP levels were only slightly affected, but addition of a thiamine transport inhibitor decreased ATP content and increased lactate production. Sharma et al. isolated the mitochondria from the brains of mice made thiamine deficient and found a 7-fold increase in protein carbonyls and an approximately 7-fold decrease in superoxide dismutase.[18] Parker et al. also studied mitochondria from the brains of thiamine-deficient rodents and saw that respiration state 3 rates fell in thiamine-deficient animals when pyruvate/malate, alpha-ketoglutarate, or glutamate were used as substrate.[19] Bennett et al. studied liver mitochondria of thiamine-deficient rats and found that oxidation of pyruvate +malate was reduced by 30% ($P < .001$), of 2-oxoglutarate by 64% ($P < .001$), and of glutamate by 77% ($P < .01$).[20] In brief, mitochondrial function is profoundly depressed by thiamin deficiency, and might be reflected by hypometabolism and synaptic dysfunction.

The reason thiamine deficiency results in decreased synthesis of ATP, contributing to synaptic hypometabolism, is because pyruvate dehydrogenase, for which thiamine is a cofactor, is necessary for the conversion of pyruvate to acetyl CoA which, via the citric acid cycle, is required for the production of the driving force for oxidative phosphorylation of adenosine diphosphate (ADP) to ATP. Despite that and the equations shown above it is, perhaps, surprising yet relevant that the decrease in ATP that is associated with thiamine deficiency is only slight. For example, McCandless et al.[21] reported that the concentrations of ATP in the cortex, cerebellum, and brain stem of thiamine-deficient rats were not significantly different from those in pair-fed controls or controls on a normal diet; and Aikawa et al. saw unchanged ATP levels in the cortex, diencephalon, and cerebellum, and only a 10.5% decrease in the brainstem.[22] As shown below, thiamine deficiency affects adversely most of the pathways leading to AD, so it could be a source of cerebral hypometabolism additional to inadequate ATP levels.

7 | CONSEQUENCES OF INCREASED REACTIVE OXYGEN SPECIES IN THIAMINE DEFICIENCY

Oxidative stress occurs if reactive oxygen species (ROS) reach abnormally high concentrations that impair redox-sensitive signaling pathways, causing calcium efflux from the endoplasmic reticulum (ER) and depressing mitochondrial function that could manifest as hypometabolism in the ^{18}F-FDG scan. Thiamine's importance for oxidative stress is because it is a cofactor for both α-ketoglutarate dehydrogenase and transketolase, thus reducing generation of NADH and limiting the actions of both the respiratory chain and antioxidant enzymes. Langlais et al. induced thiamine deficiency in rats that led to an increase of ROS by 34.9% in the thalamus and by 19% in the cerebral cortex ($P < .05$ for both).[23] Chauhan et al. made mice thiamine deficient and saw reductions of 86% in glutathione reductase, of 72% in reduced glutathione, and of 84% in superoxide dismutase.[24] In the brains of thiamine-deficient mice, Sharma et al. also saw major decreases in levels of reduced glutathione, superoxide dismutase, and catalase, and increases in levels of glutathione reductase and protein carbonyls.[18] Thus, oxidative stress is a factor that might produce synaptic dysfunction in ways besides deficiency of ATP.

8 | LACTIC ACIDOSIS AND KETOACIDOSIS IN THE BRAIN

Lactate can contribute up to ≈60% to oxidative brain metabolism, with glucose providing the rest. The neuronal monocarboxylate transporter is proton-coupled, therefore its increased use for lactate production may result in intracellular acidification. Reports of patients having both thiamine deficiency and cerebral acidosis are mostly from cases in the past when supplementary thiamine for individuals undergoing hemodialysis was unavailable and consequently, many of them had profound thiamine deficiency and became severely symptomatic. Administration of thiamine reduced their lactate levels and gave a statistically significant decrease in mortality.[25] Thiamine deficiency, which is common in the general population especially in the elderly, is therefore a risk factor for cerebral acidosis.

9 | THIAMINE AND THE CEREBRAL DEPOSITION OF AMYLOID

Thiamine deficiency also contributes to amyloid deposition. Karuppagounder et al. presented findings from a mouse model of AD, showing that thiamine deficiency significantly decreased α-ketoglutarate dehydrogenase activity in the brains; exacerbated amyloid plaque pathology, with a 2-fold increase in areas of plaques in the hippocampus; and produced a 3-fold increase in Aβ1-42 levels in formic acid extracts of brain.[26] Similar data from mice fed a thiamine-deficient diet were made by Gong et al.; the mice had increased levels of Aβ1-40 in the cerebral cortex.[27] Calingasan et al. examined brains of thiamine-deficient rats and saw a 40% increase of APP-like protein in their

thalami although no deposition of Aβ17-24 was seen.[28] Thiamine-deficient, APP/PS1 transgenic mice, studied by Zhao et al., had a 3-fold increase in cerebral amyloid plaques, which even in thiamine-deficient wild-type mice were increased by 1.55-fold ($P < .001$).[29] The opposite finding, of decreased amyloid plaques, occurred when benfotiamine, which is a thiamine derivative with better bioavailability, was administered to a mouse model of AD;[30] benfotiamine also reversed the decrease in spine densities caused by Aβ added to cultured hippocampal neurons. Surprisingly, in view of the above data, and their finding that mice with TPK knockout had deposition of Aβ, Sang et al. found that reduction of thiamine diphosphate correlated strongly with brain glucose hypometabolism but showed no significant correlations between blood thiamine diphosphate levels and amyloid deposition in brains of patients with AD as evaluated by Pittsburgh compound B positron emission tomography (PET) scanning.[31]

10 | THIAMINE AND CEREBRAL DEPOSITION OF TAU

Hyperphosphorylation of tau causing dystrophic neurites occurs when thiamine is deficient, and is lessened when that deficiency is corrected. Thus, thiamine-deficient mice had dystrophic neurites containing hyperphosphorylated tau[30,32] and the observations, already mentioned, by Sang et al., of mice with thiamine deficiency caused by TPK knockdown, showed that in addition to amyloid deposition they also had hyperphosphorylated tau.[31] Zhang et al. showed that correcting thiamine deficiency reduced the numbers of cells containing hyperphosphorylated tau.[4]

11 | THIAMINE AND SYNAPTIC DYSFUNCTION

The focus of this article concerns synaptic dysfunction, which several neurophysiological studies show as affected by lactic acidosis. Schurr et al. exposed hippocampal slices to iodoacetate that inhibits glycolysis; the now synaptically silent slices were reactivated with lactate, indicating that lactate was metabolized directly via pyruvate to enter the tricarboxylic acid cycle.[33] Hollnagel et al. explored lactate use in slice preparations of the hippocampus, and focused on two fast network rhythms: gamma oscillations (30–70 Hz), which support action potential timing and synaptic plasticity; and sharp wave-ripples (> 180 Hz), which assist in memory consolidation.[34] Both rely on precise synaptic transmission between excitatory pyramidal cells and inhibitory GABAergic interneurons. Hollnagel et al. induced these cortical rhythms in the brain slices and found that lactate disturbed them; this is because presynaptic terminals should upregulate glycolysis during sustained neuronal activity but lactic acidosis suppresses glutamate receptors and enhances GABA-A receptors. Walz and Harold measured the presynaptic fiber volley and the population excitatory postsynaptic potential, and the extracellular pH, in the CA1 layer of hippocampal slices.[35] The high levels of lactate released by synapses suppressed synaptic transmission irreversibly if the acidosis reached pH 6.7 (normal intracellular pH is 6.9–7.2). Tang et al. also saw that the N-methyl-D-aspartic acid (NMDA)-activated current was suppressed by extracellular acidosis, and it was associated with changes in the NMDAR channel, which has high permeability to Ca^{2+}.[36] Tang et al. suggested that the modulation of the NMDAR channel may be a protective mechanism that regulates influx of calcium. The sigmoid curve describing the NMDA current versus pH is very steep, making the NMDA channel highly sensitive to small perturbations of H^+, so that a small increase in acidosis produces a large decrease in NMDA-activated current. Hsu et al. confirmed that excitatory postsynaptic potentials were significantly reduced by acidosis, which depressed the sensitivity to NMDA but not to AMPA.[37] In many synaptic systems, long-term potentiation (LTP), which is a persistent increase in synaptic strength after high-frequency stimulation of a synapse, is dependent on intact function of NMDARs. Velíšek also found that acidification of hippocampal slices suppressed the efficacy of normal, low-frequency synaptic transmission and prevented the induction of LTP.[38] In brief, thiamine deficiency causes cerebral acidosis, which might result in synaptic dysfunction. Because synaptic use of lactate occurs when glycolysis is inadequate to maintain metabolism, it would be shown as synaptic hypometabolism in the ^{18}F-FDG PET scan.

12 | THIAMINE AND NEUROTRANSMISSION

Griffith and Bondareff observed that synaptic vesicles contained thiamine pyrophosphatase, which might contribute to synaptic hypometabolism because reducing the level of thiamine pyrophosphate also decreases formation of ATP.[39] It also decreases acetyl CoA and, therefore, of acetylcholine that is synthesized from acetyl CoA and choline in a reaction catalyzed by choline acetyl transferase. After rats ate a diet deficient in thiamine for 5 weeks, Heinrich et al. examined their brains and found acetyl choline levels were reduced by 35.6% ($P < .05$) compared to rats fed a normal diet; and transketolase (for which thiamine pyrophosphate is a cofactor), was even more profoundly, 64.5%, reduced.[40] After 25 days on a thiamine-deficient diet, Nakagawasai et al. saw that rats had significant impairment of avoidance learning and choline acetyltransferase became markedly decreased in the cortex and hippocampus.[41] Gong et al. also saw decreased acetylcholine transferase in the cerebral cortex of mice fed a thiamine-deficient diet.[27] A general contribution by thiamine deficiency to synaptic and neural circuit defects was demonstrated in experiments by Yu et al.[42] Using RNAi to downregulate thiamine phosphokinase, thereby reducing thiamine diphosphate levels, they saw a 31% decrease in the density of dendritic spines in cultured hippocampal neurons and a significantly reduced strength of hippocampal synaptic transmission as measured by the field excitatory postsynaptic potential (fEPSP). Further, LTP induction, which requires activation of postsynaptic NMDARs and AMPARs, was significantly suppressed, indicating impaired synaptic plasticity in thiamine deficiency. The decreased density of dendritic spines was fully rescued when they used neurons that overexpressed RNAi-resistant thiamine phosphokinase. Synaptosomes contain both postsynaptic and

presynaptic components and are surrounded by a plasma membrane. Parkhomenko et al. isolated synaptosomes from rat brain by differential ultracentrifugation, and found that a thiamine binding protein was present in both the plasma membrane and synaptic vesicles, together with thiamine mono-, di-, and tri-phosphates.[43] Eder et al. studied isolated synaptosomes from nerve terminals of the electric organ of the marbled electric ray (Torpedo marmorata) and found that they contained a very high amount of thiamine, 55% of which was in the form of the triphosphate, suggesting that thiamine is involved in the process of acetyl choline release.[44] Further evidence was provided by Csillik et al., from histochemical electron micrographs that showed thiamine triphosphatase in close apposition with synaptic vesicles in the rat spinal cord.[45] However, it is important to note that thiamine may variably, either positively or negatively, affect different modes of acetyl choline release; one should be cautious about holding that thiamine is always a positive influence and that its absence is deleterious. The details of this issue are discussed in Dunant.[46] Thiamine triphosphate is also a cofactor for the action of α-ketoglutarate dehydrogenase, which Gibson et al. found was 35% less in 109 AD brains than in control brains; concurrently, choline acetyl transferase was 59% lower in AD brains than controls and there was a progressive and significant decrease in α-ketoglutarate dehydrogenase levels with worsening Clinical Dementia Rating (CDR) scores.[47] Because the action of α-ketoglutarate dehydrogenase requires thiamine pyrophosphate, which is low in the AD brain (see above), as a cofactor, one may infer that thiamine pyrophosphate depletion is responsible for the worsened CDR scores. Further, pyruvate dehydrogenase, another enzyme for which thiamine pyrophosphate is a cofactor, was seen by Sorbi et al. as having its activity reduced by 38% in the frontal cortex of five AD brains.[48]

13 | THE BENEFIT TO COGNITION OF THIAMINE AND THIAMINE DERIVATIVES, IS SHOWN BY THEIR LOW LEVELS IN BLOOD AND BRAIN OF AD PATIENTS

Comparing 43 AD patients and 338 controls, there was a 27.8% decrease in AD of blood thiamine diphosphate (85.0 vs. 117.7 nmol/L $P < .001$).[49] Glasø et al. compared blood levels in 20 women with AD and 18 healthy women, and also saw in the AD patients a 39% reduction of thiamine and a 23% reduction in thiamine diphosphate ($P < .05$ for both compounds).[50] Héroux et al. examined blood levels in the temporal cortex taken from six patients with AD and eight age-matched controls, and found in AD a 67% decreased level of TMPase with a concordant increase of TMP and decrease of TDP.[51] Those findings must reflect the greatly decreased reductions of 2-ketoglutarate dehydrogenase complex in the AD brains mentioned above. Likewise, Sang et al. reported (in a preprint publication not yet peer reviewed) that thiamine phosphokinase (TPK) levels in the frontal cortex from 12 AD patients were reduced by 30% ($P < .001$), and that TPK gene knockout (ko) in the mice caused cerebral glucose hypometabolism, Aβ deposition, tau hyperphosphorylation, neuroinflammation, and neuronal loss and brain atrophy.[3] In a cross-species correlation analysis, Sang et al. found similar changes in gene profiling between the ko mice and AD patients; they concluded that the deficiency of brain TPK, a key enzyme for TDP synthesis, is specific to AD. In brief, evidence supports the possibility that deficiency in brain levels of thiamine or its products may contribute to the synaptic hypometabolism seen in some persons who will later develop cognitive loss and AD.

14 | THIAMINE DEFICIENCY AFFECTS ASTROCYTES, ENDOTHELIAL CELLS, AND THE BLOOD BRAIN BARRIER

There is an intimate, anatomical connection between synapses, astrocytes, and the cerebral microcirculation; and the astrocytic processes that surround the synapse, contribute to synaptic connectivity, and synaptic plasticity.[52] So, it is unsurprising that all three components might be affected by thiamine deficiency. In a very early study, Collins placed rats on a thiamine-deficient diet and saw, by electron microscopy, cellular abnormalities in both astrocytes and oligodendrocytes.[53] Maintaining low extracellular glutamate so as to prevent excitotoxic cell death requires removal of glutamate from the synaptic cleft, an important mechanism of which is the binding of glutamate by the several astrocytic glutamate transporters, making the astrocyte a major regulator of glutamatergic neurotransmission. In rats made deficient in thiamine, Hazell et al. found a 71% and 51% decrease, respectively, in levels of the astrocytic glutamate transporters GLT-1 and GLAST;[54] and in the frontal cortex of patients with Wernicke-Korsakoff encephalopathy, which is caused by severe thiamine deficiency, other astrocytic glutamate transporters, EEA1 and EEA2, were reduced by 62% and 71%, respectively.[55]

The BBB is formed by endothelial cells that, circumferentially in the capillary, are joined by proteins producing very tight, intercellular junctions; the other component of the BBB is the basement membrane. Montagne et al. described their own studies and those of several others that demonstrated BBB breakdown and dysfunction in AD.[56] In his studies of rats who were deficient in thiamine, Collins saw abnormalities in the capillary basement membrane, which was widened and had reduced electron density.[53] The abnormalities were only seen when an abnormal glial cell was adjacent to a capillary. Using horseradish peroxidase as a marker, Manz and Robertson showed a permeable BBB in thiamine-deficient rats;[57] using albumin as a marker of BBB permeation in the brains of mice, Harata and Iwasaki saw massive extravasation of albumin by the 10th day of taking a thiamine-deficient diet.[58]

15 | ROLE FOR THIAMINE IN TREATMENT OF ESTABLISHED AD, AND FOR PREVENTION OF COGNITIVE LOSS IN PREDISPOSED ELDERLY PERSONS

In addition to thiamine levels being low in AD, showing a possible connection between thiamine and cognitive loss, variable benefit to

cognition has been seen from using thiamine therapeutically. One of the first trials of thiamine in AD was by Blass et al.: a crossover administration for 3 months of thiamine (a large dose, 1.0G tid) followed by 3 months of placebo, or vice versa, in just 11 patients.[59] There was a 5% increase ($P < .001$) in the MMSE in the thiamine-treated patients; but a later, 1-year study from the same clinic using a different group of 15 AD patients and the same dose of thiamine, showed no benefit.[60] After that, Meador et al. reported results from two trials using different doses of thiamine given in a double blind, randomized, placebo controlled, crossover study for 6 months in each trial.[61] The first trial, in 17 patients, showed that the Alzheimer's Disease Assessment Scale (ADAS) score was significantly improved ($P < .02$) with the thiamine compared to the placebo; MMSE showed no difference. The second trial in 17 patients that included six from the first trial, used an initial phase of an open label dose with up to 6G thiamine daily to determine the tolerated dose; that was followed by a single blind placebo for 1 month followed by the tolerated dose for 1 month; after that, thiamine dose was increased by 0.5G daily to a maximum of 8G/day. For months 1 (4G/day), 6 (6.5G/day), and 7 (7G/day), there were significant improvements in the ADAS score but in months 8 to 13 (6.5–8.0G/day and with fewer patients completing the study) thiamine gave no benefit. Fursultiamine is a thiamine derivative with better bioavailability than unmodified thiamine; a single dose gave a 300% increase in the area under the curve of plasma thiamine.[62] In a 12 weeks' open trial, the next study gave 100 mg/day of fursultiamine, to nine AD patients including six with mild disease (MMSE mean 21.3, dementia rating score mean = 22.7) and three with severe disease (MMSE mean 9.0, dementia rating score mean = 5.7).[63] Improvements were noted in four of the six with mild disease either in the MMSE or in one of the two dementia rating scales used; none of the three with severe disease showed improvement. Benfotiamine, another thiamine derivative, also with better bioavailability than unmodified thiamine, was used in a recent 12 months' study by Gibson et al. that required patients with AD to have MMSE > 21.[64] There were 37 assigned to placebo and 34 to benfotiamine 300 mg bid. The ADAS-cog scale was the primary outcome measurement, and although this was 43% lower in the benfotiamine group it was non-significant ($P = .125$); however, worsening in the CDR scale was 77% lower in the benfotiamine group ($P = .034$). The 12-month treatment with benfotiamine significantly elevated blood thiamine by 161-fold above baseline (also thiamine diphosphate by 2-fold and thiamine monophosphate by 5-fold). There were no significant differences in the uptake of ^{18}F-FDG. In brief, there are mixed results reported for the benefit of thiamine supplements in established AD. The most recent trial by Gibson et al.[64] is the most useful for two reasons. First, the inclusion criteria required all patients to have MMSE > 21, so their dementia was mild and the patients were not thiamine deficient at baseline, yet the treatment enormously amplified their blood thiamine level; second, although the primary outcome criterion of CDR scale was not significantly benefitted despite being 43% better than in the placebo group, and the uptake of ^{18}F-FDG did not improve, yet the CDR score clearly benefitted.

Overall, it is quite possible that the mixed performance of thiamine in the treatment of established AD is because of the difficulty of reversing a condition that has multiple aberrant biochemical pathways. The last-mentioned results above support the possibility that thiamine treatment might be successful if administered before the process has started to unfold, when fewer biochemical pathways are involved.

The data provided in this paragraph and in the paragraph concerning thiamine in established AD demonstrate the important part played by thiamine in the process underpinning cognitive loss.

16 | CLINICAL TRIAL TO VALIDATE THE USE OF THIAMINE TO PREVENT ALZHEIMER'S DISEASE FROM COMMENCING

The range of evidence presented above is a mosaic that provides a picture suggesting that supplementary thiamine administered to elderly persons with currently normal cognition but at risk of eventual AD, has the reasonable potential to prevent future cognitive loss from starting, thus preventing AD. That potential must be validated by a clinical trial. Such a trial would require a duration of 3 to 5 years, several thousand participants with an age range of 65 to 85, cerebral scans that demonstrate depositions of either amyloid or tau, and neuropsychological tests showing cognition at enrolment to be in the ranges of normal; the neuropsychological tests would be repeated at yearly intervals. Participants would be randomized to receive either thiamine or matching placebo. To determine the appropriate dosage, those persons randomized to use thiamine would be allocated to one of three doses, low (5 mgs), medium (20 mgs), or high (100 mgs), taken once daily. A power calculation would determine the number in each arm needed to show with $P < .05$, that a 30% reduction in subsequent dementia, gives an 80% power to avoid a type 1 error. Despite being arduous and financially costly, a trial is justified by the enormous cost to the sufferers, their families and caregivers, and society.

17 | CONCLUSIONS AND SUMMARY

1. Cerebral PET scans using appropriate labels identifies those elderly persons whose cognition is currently normal but who are at risk of subsequent cognitive loss that may end in AD.
2. Synaptic hypometabolism is present in most of those elderlies who are at risk of later AD.
3. Although inadequate ATP may cause synaptic hypometabolism, that may not be the entire cause because, in fact, measurements in some of the at-risk persons have shown normal ATP levels.
4. Thiamine deficiency is often seen in elderly, ambulatory persons, although its frequency is uncertain. Its consequences may include hypometabolism, mitochondrial depression, oxidative stress, lactic acidosis and cerebral acidosis, amyloid deposition, tau deposition, synaptic dysfunction and abnormal neuro-transmission, astrocyte function, and BBB integrity, all of which are features of AD.
5. Although the benefits of administering thiamine to patients with AD or MCI have been mixed, it is likely that reversing or halting established cognitive loss or dementia might be far less likely to

succeed than preventing the onset of cognitive loss at a time when the number of aberrant biochemical pathways is far fewer.

6. Providing a thiamine supplement to elderly persons with normal cognition may have the potential to prevent subsequent cognitive loss and eventual dementia. That potential requires validation in a randomized clinical trial.

CONFLICTS OF INTEREST

No funding was received for this study, either from the public or private domain. There are no conflicts of interest. No human subjects were involved; therefore, no consents were necessary.

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